Work in Progress: Please do not quote without permission

Assessing Generalisability in Economic Evaluation Alongside Multicentre Randomised Controlled Trials: A Systematic Methods Review

Francis Pang[1], Andrea Manca[1], Mark Sculpher[1], Mike Drummond[1]
John Nixon[2], Jimmy Christie[2]

1. Centre for Health Economics, University of York
2. NHS Centre for Reviews and Dissemination, University of York

Abstract

An NHS HTA methodology project on methods to assess and to improve generalisability in economic evaluation was commissioned to identify the methods adopted and the issues that influence generalisability in economic evaluation from study to practice, between locations and over time. As part of the project, this paper discusses issues relating to the generalisability of economic evaluations conducted alongside multi-centre randomised clinical trials. A review of the NHS Economic Evaluation Database between 1995-2001 was conducted to identify cost-effectiveness or cost-utility studies that have been performed alongside multinational or multicentre trials. From 107 articles identified, 101 were considered relevant for inclusion. Information on studies was extracted using a *pro forma* designed to assess how the generalisability of an economic evaluation is reported, analytical methods relating to generalisability within the trial and analytical methods to adjust trial results to non-trial contexts. Data were extracted by two reviewers working independently, with checks performed by each reviewer on 10% of the other reviewer's sample. This research is a step towards development of a framework for critically assessing the generalisability of economic evaluations and for advising on issues to consider in designing, analysing and presenting studies to increase the generalisability of the results.

Paper presented to the 60th UK Health Economists' Study Group Conference, University of East Anglia, Norwich, UK, 7-9th January 2002

1. Background

1.1 The concept of generalisability in economic evaluation

The growth in the publication of economic evaluations of health care interventions and treatments (Elixhauser et al., 1998; Phelps 1998) has raised concerns about the methodological rigour of these studies and their value to decision makers (Drummond et al., 1997). One pertinent aspect of economic evaluation is the extent to which the results of studies are generalisable across different settings and patient groups, and are stable over time (Bryan et al., 1998; Drummond et al., 1992; Johnston et al, 1998; Mason 1997; O'Brien 1997; Phelps 1997). Although these issues have also been raised in the context of clinical studies (Altman et al., 1998), the results of economic evaluations are viewed as being particularly sensitive to factors that vary geographically and temporally, hence limiting their generalisability.

Economic appraisal involves the measurement and valuation of the resource and non-resource consequences of interventions to assess their relative value for money (Drummond et al., 1996; Gold et al., 1996). The numerous parameter estimates within a given study are likely to be influenced by the setting from which the data were taken, where 'setting' can refer to geographical location and type of health care facility. Both of these factors will influence the availability and use of health and social care resources. In addition they will determine the sample population which will affect the costs and benefits of health care interventions (e.g. epidemiology, disease severity, demographic and cultural characteristics and socio-economic status).

Various authors have suggested factors that may limit generalisability in economic evaluation (Drummond et al., 1992; O'Brien 1997). These include

- *Demography and epidemiology of disease*. For example, the prior risk of disease will influence the cost-effectiveness of screening and prevention programmes and will vary by setting.
- *Clinical practice and conventions*. For example, the 'standard care' comparator against which to evaluate the cost-effectiveness of a new therapy will vary and potentially compromise the generalisability of a study. An important aspect of this threat to generalisability is the difference in practice that may exist between centres that typically become involved with randomised controlled trials (e.g. teaching centres) and non-research centres.
- *Incentives and regulations facing health care providers*. For example, a study undertaken in hospitals which are reimbursed on a fee-for-service basis may observe a different pattern of resource use (and health outcomes) than would have been demonstrated in centres operating under fixed remuneration or global budgets.
- *Relative price levels*. For example, the price of drugs and staff salaries differ by country; and the value of land and buildings can differ markedly between centres within countries.

- *Individual preferences*. The benefits of health care are a function of the outcomes generated and of the preferences of individuals regarding those outcomes. These preferences are likely to vary by location (e.g. due to cultural and income differences) (Brouwer 1997; Donaldson et al., 1998; Sculpher et al., 1999).
- *Opportunity cost of resources*. The mix of resources available for health care varies between and within country which affects the extent to which a given incremental cost-effectiveness ratio will be considered acceptable.

Most taxonomies identified have focused on the sensitivity of the results of economic evaluations to parameters that vary by location. However, each of these potential limitations to generalisability could work over time as well as geographically. For example, as the duration of stay in hospital following open surgery has fallen over a period of years, the potential for new minimal access surgical techniques to be more cost-effective than standard surgery has declined (Sculpher 1993). This has applied in particular to hernia repair, for example, where open repair is now invariably undertaken on a day-case basis in the NHS, thus limiting the scope for laparoscopic repair to generate cost savings (Wellwood et al., 1998).

In addition, the production and diffusion of new information will influence the durability of the results of economic studies. For example, an early cost-effectiveness analysis of erythropoietin in end-stage renal failure found limited evidence of cost-effectiveness (Leese et al., 1992), but this picture changed as experience and data emerged indicating more effective lower doses of EPO and higher costs associated with improved transfusion therapy (Matheson et al., 1993; Steven et al., 1992).

Although there is general agreement about the range of factors that may limit the generalisability of economic studies, few empirical studies have provided evidence that these differences can be important (Drummond et al., 1992; Drummond et al., 1994; Johnston et al., 1998; Menzin et al., 1996; Willke et al., 1998). However, there has been little analytical research to explore the causal relationships between the factors outlined above and the absolute difference or direction of change in estimates of cost and effect in studies undertaken in different settings and at different points of time.

The sensitivity of cost and outcomes to factors that vary by time and place raises a series of methodological questions about the analysis, presentation and interpretation of economic data. These concern how to optimise generalisability and facilitate transferability between geographical locations and between time periods.

1.2 Generalisability in trial-based economic evaluation

Most of the methods literature on generalisability has focused on issues relating to economic studies undertaken in parallel ('piggybacked on') with randomised controlled trials (RCTs) (Adams et al., 1992; Coyle et al., 1998; Drummond et al., 1991). Multinational or multicentre clinical trials are often used as an

experimental vehicle in that they offer several potential advantages over single centre trials. These include the opportunity to ensure a speedy recruitment of a sufficient number of patients for the clinical endpoints of the study, the opportunity to improve the representativeness of the study population for promoting interest among clinical opinion leaders and the opportunity for meeting the needs of regulatory agencies in different countries. In addition, multicentre/multinational trials provide a means for exploring how costs, effects and cost-effectiveness vary by location.

A number of papers have considered the question of how to analyse economic evaluations alongside international trials (Johnston et al., 1998; Schulman et al., 1996; Willke et al., 1998). These include multi-national trials where potential differences between countries in clinical practice (hence resource use and outcomes) and unit costs limit the applicability of results to any one country; or trials undertaken in one country where attempts are made to transfer their results to one or more other locations. Several approaches have been advocated for the analysis of these studies including (a) the substitution of those parameter estimates felt to be sensitive to variability between countries with country-specific data within a modelling framework (Menzin et al., 1996); (b) the use of regression analysis to estimate costs and effects whilst controlling for between-country variation (Willke et al., 1998); and (c) the use of tests for heterogeneity to check for outcome-centre interactions, where absence of interactions is considered justification for pooling data (Cook et al., 1997).

Generalisability issues regarding multinational clinical trials apply equally to generalisation to (i) individual centres in multicentre trials conducted in one country and (ii) individual countries in multinational trials. Naturally these issues maybe embedded within one another when one wants to make decisions for individual centres in individual countries that participated in a multinational trial.

1.3 Rationale for the review

Methods in economic evaluation are rapidly developing, in particular statistical issues relating to the analysis of patient-level datasets such as clinical trials (Heyse et al., 2001). Currently, there is uncertainty regarding the appropriate quantitative methods to assess the variability of cost-effectiveness between centres and countries in trial-based economic studies. However, there remains an important role for careful reporting of these studies to enable the decision maker to assess the relevance of the results for his/her specific location.

We undertook a systematic review of published economic evaluations alongside multicentre randomised controlled trials to address three questions:

- Are studies reporting their results in a manner which allows decision makers to assess their generalisability and their relevance to their own location?
- What methods are being used to explore the variability of results between those locations participating in the trial?
- What methods are being used to assess the generalisability of results to locations not participating in the trial.

These questions were addressed by the development of a data extraction instrument to apply to all appropriate studies identified.

2. Methods

2.1 Inclusion criteria

The aim was to identify full economic evaluations which were undertaken alongside a multicentre or multinational randomised controlled trial. We focused on the period 1995-2001 and considered papers in all languages.

2.2 Search strategy

We searched a sub-group of the NHS Economic Evaluation Database consisting of *type A* studies. These are, economic evaluations based on a single study (e.g. randomised controlled trial, nonrandomised trial with concurrent controls, cohort study, case-control study, study with historical controls, before and after study in one group of patients, case-series, etc.). We added the following search-terms: 'multicentre', 'multinational', 'randomised controlled trials', 'clinical trials' . A data extraction instrument was developed for the review to focus on the questions listed above. The instrument is shown in Appendix 1.

The first section of the report focused on the way that the methods used in the trial in general, and the economic evaluation in particular, as well as the study's results were reported. The purpose of the section was to assess whether the study provided sufficient information for a decision maker to establish the relevant of the analysis to their specific setting. In total 21 items were included in this section, covering the following themes:

- Information provided in the interventions being evaluated
- Information provided on the patient population from which the trial sample was taken
- Information on the trial sample
- Information on the centres and countries in the trial
- The extent to which data used in the economic evaluation were collected in a sub-group of trial patients
- The perspective of the economic study
- The duration of recruitment and follow-up
- Details of the unit costs used
- Details of any preference (utility) data used

The second section of the instrument considered any analytical methods that had been adopted to assess the extent to which the economic results varied between the centres/countries participating in the study, between trial centre and routine (non-trial) practice and also the extent to which there was variability over time in the study. Given uncertainty in appropriate methods, the focus here was more on describing these methods rather than establishing whether

'good practice' had been adhered to. A total of 10 items were incorporated into this section to extract information on both quantitative and descriptive methods that had been employed.

The final section of the instrument was designed to extract information on any methods that were used to adapt the results of the trial-based analysis to contexts outside the trial, where these could relate to non-trial locations, non-trial practice or to different time periods.

2.3 Data extraction

Information was extracted using the instrument by two reviewers (FP and AM) working independently of each other. Data were entered into a database for analysis using STATA 7.0, with checks conducted by each reviewer on 10% of the other reviewer's sample.

3. Results

Of the initial sample of 107 studies initially identified, 101 studies satisfied the criteria for inclusion (these are listed in Appendix 2). 6 studies were rejected because they were models (n=4), before and after studies (n=1), and cohort studies (n=1). The following sections provide a more detailed description of the results.

3.1 Data presentation and reporting

Type of randomised trial
Of the entire sample, 73.3% (n=74) of the economic studies were conducted alongside multicentre (national) trials, and the remaining 26.7% were carried out within multinational trials (n=27).

Type of economic analysis
As expected, cost-effectiveness was the most popular form of analysis (n=40), followed by cost-consequence (n=27), and cost-minimisation analysis (n=25). Cost-utility (n=7) and cost-benefit analyses (n=6) were less prevalent in the sample. This total is greater than 101 because some papers conducted more than one form of economic analysis.

Basis of sampling
In the review we aimed to assess whether any form of sampling was performed on resource use, clinical outcome, and quality of life data. Among the studies included in this review, 19.8% were characterised by some form of sampling for resource use (n=20). Of these, 9 studies used a sub-group of patients, 6 looked at resource use from a sub-group of centres, 1 international study collected data from only one country, 3 studies sampled patients from different centres, and one study gathered data outside the trial.

The collection of clinical outcome data was less characterised by sampling, with only 5 studies obtaining data from a subset of patients, and 3 collecting data

from a subset of centres. Among those studies collecting health related quality of life data, no sampling was undertaken.

Reporting of numbers of centres, patients and countries/ jurisdictions
An important piece of information that was considered relevant was the number of centres, countries, and patients in the economic study. From the review it appears that 83 articles (82.2%) reported the number of centres in the study where costs and effectiveness data were collected. All studies reported the number of patients enrolled in the trial, and 99 stated the number of countries participating in the study.

Alternatives described and justified
78 studies (77.2%) provided a clear description and justification of the alternative interventions being compared, whereas the remainder of the studies provided only a description of the comparators used.

Inclusion/exclusion criteria
78 studies (77.2%) listed the inclusion and exclusion criteria for the study population, and 72 studies (71.3%) described the baseline characteristics of the patient sample. The most frequently reported were *age* (n=66)*, gender* (n=57), *disease severity* (n=39)*, and co-morbidities* (n=23). However, only 2 studies assessed the representativeness of the study sample to the study population in the trial centres.

Economic study perspective
The economic study perspective was defined in only 42 studies (3.9%), and the analysis was consistent with this perspective in 36 of these 42 studies.

Study setting
In 91 articles, a definition of the study setting was provided, but only 3 papers described the characteristics of the health care system(s) where the economic analysis was conducted. In addition, only 7 studies reported one or more centre-specific characteristics. Centre-specific characteristics reported included professionals' experience (n=1), teaching hospital (n=3), size of the centre (n=3) and volume of cases (n=2).

Duration of recruitment and follow-up
While the duration of the follow up period was reported in the majority of the reviewed papers (n=87), many failed to report the duration of the recruitment period (n=29).

Details about unit costs
Almost every study reported the currency (n=99) and the sources of unit costs (n=92), but only two thirds of the sample provided information regarding the year of costing (n=76). In addition, it was surprising to see that only 25 studies (2.4.7%) reported resource use and unit costs separately, with the rest of the sample reporting them partially separate (n=31), or combined (n=45). Half of the papers where currency conversion was used (n=37) failed to give details of methods and sources for conversion.

3.2 Analytical methods relating to generalisability within the trial

Few studies used analytical methods to explore generalisability in their results. Only 26 studies (25.7%) compared their results with similar studies, although some of those that did not claim that their study was the first one in that clinical area. 5 of these 26 studies set their results in the context to other independent interventions (e.g. in a league table).

Formal quantitative methods to explore the variability of the results were used in

5 studies to look at variability from place to place, and in 1 paper to assess the generalisability from study to practice. None of the studies in the sample attempted to use methods to assess the variability of the results over time.
In this review, formal quantitative methods refers to use of mathematical methods used to investigate the variability in the results such as regression analysis and excludes routine testing of the robustness of particular parameters (e.g. unit costs) through the use of sensitivity analysis. In terms of descriptive analysis, there was only one example observed in the sample. In this review, descriptive analysis refers to discussion of the variation in results by the authors and may encompass the use of checklists.

In terms of sensitivity analysis, half of the studies in the sample did not undertake any assessment to identify the sources of variation in their results, and 16 studies did not find any element of variation. Among the sources identified to have an impact on the stability of the results were absolute/relative costs or prices (n=17), clinical practice (n=16), and compliance (n=6).

3.3 Analytical methods to adjust trial results to non-trial context(s)

Finally there were no examples of the application of methods to adjust trial results to non-trial contexts in terms of *location*, *study to practice*, or *over time*.

4. Discussion

4.1 Study reporting

From the results obtained from this review, the quality of data presentation and reporting, for the purposes of allowing decision makers to assess the generalisability of the economic evaluation results, was mixed.

The were a number of encouraging findings:

- The reporting of the alternatives was acceptable with three-quarters of papers providing a clear description and justification. Reporting of comparators is considered important since they are likely to vary between countries as (1) the types of resources available can differ among health care systems e.g. a drug might be licensed in one country but not in another; (2)

medical guidelines can differ from one country to another or from one setting to another; (3) the use of a given therapy may change over time especially when new scientific data becomes available; (4) the relative costs of resources might favour the least expensive interventions.

- The majority of studies (82.2%) reported the number of centres in the study where costs and effectiveness data were collected. All studies reported the number of patients enrolled in the trial, and 99 stated the number of countries participating in the study.

- Over 70% of studies listed the inclusion and exclusion criteria for the study population, and described the baseline characteristics of the patient sample.

- The duration of the follow-up period was reported in the majority of the reviewed papers (n=87).

- Almost every study reported the currency (n=99) and the sources (n=92) of unit cost data.

There are some clear limitations on how studies are reported, however:

- Only 2 studies assessed the representativeness of the study sample to the study population in the trial centres. If only a small proportion of patients are recruited into trials from amongst those eligible (i.e. fulfilling the inclusion and exclusion criteria), and the characteristics of those included are not representative of the population, the generalisability of the study would probably be compromised.

- The economic study perspective was defined in only 42 studies (3.9%), and the analysis was consistent with this perspective in 36 of these 42 studies. Given the importance of perspective as a basic method in economic evaluation, this is a surprising result. If analysts neglect to provide this sort of information, the onus is on the decision maker to interpret the perspective from available information on costs and effects.

- In 91 articles, a definition of the study setting was provided, but only 3 papers described the characteristics of the health care system(s) where the economic analysis was conducted. In addition, only 7 studies reported one or more centre-specific characteristics. Although this is perhaps as would be expected, it can be argued that the presentation of this sort of information helps a decision maker interpret the study's relevance to their setting. Previously it has been suggested that there should be more careful selection of centres based on their economic characteristics and the definition of what a representative centre can be taken to be (Johnston et al., 1997).

- Few studies reported the duration of the recruitment period (n=29). Again, this may not be common in economic studies, but it is important information to allow the reader to judge how clinical practice might have changed. If a

trial has recruited over a long period, then 'background' clinical practice may have altered. This is a particular concern with surgical interventions where a learning curve is expected, and in studies where a loosely defined 'usual practice' is the comparator.

- Only two thirds of the sample provided information regarding the year of costing (n=76). This may not be serious if unit costs are reported in sufficient detail for the decision maker to establish how close they are to their own locations.

- A surprising result was that only 25 studies (24.7%) reported resource use and unit costs separately, with the rest of the sample reporting them partially separate (n=31), or combined (n=45). The separate reporting of unit costs and resource use is widely considered 'good practice' (e.g. Drummond et al., 1997; Gold et al., 1996), and a failure to do this limits the decision maker in interpreting the generalisability of the results, and would probably preclude any adjustment of cost results to a different location.

- Half of the papers where currency conversion was used (n=37) failed to give details of methods and sources for conversion.

Further development of what constitutes 'good reporting' is required. In the past, the space constraints in journals (particularly clinical ones) have placed limitations on the sorts of detail that a decision maker might need to assess generalisability. However, some journals now provide an opportunity to place more information on a study on a web site. Technical reports can also be made available (via the authors) to extend the amount of information about the study.

4.2 Analytical methods

The use of quantitative and descriptive methods to explore variability is sparse, and no study employed analytical methods to adjust study results to non-trial context(s). There may be a number of reasons for this. First, a large part of the studies included in this review were published between 1995 and 1998 and some of the methodological contributions in this field were still to be published. Secondly, it is likely that editorial needs may have limited the scope for exploratory work within the main economic paper. For example the main economic analysis of a trial of Trilazad mesylate for aneurysmal subarachnoid hemorrhage has been reported in a non-economics journal (Glick et al., 1998) and further exploratory work in economics journals (Willke et al, 1998; Schulman et al., 1998). Thirdly funding for the economic study may be specific to the original context and therefore adjustment to non-trial contexts may not be within the interests or the responsibility of the funder. Finally, the focus of the paper may be clinical and the economic analysis was a secondary consideration.

The results of this review seem to be consistent with other reviews that have been conducted to describe variation between locations and over time. Walker and colleagues (2000) conducted a review of economic evaluations of control

strategies against parasitic diseases in terms of internal and external validity. 7 of the studies explicitly discussed the generalisability of results to other settings. Four of these provided blanket statements advocating the implementation of a new intervention without any discussion as to the applicability of their results to different economic or epidemiologic settings. In three studies, generalisability was examined through the use of itemised cost menus in which the unit costs of inputs could be changed to reflect those of other countries or regions.

Briggs and colleagues (1995) undertook a structured review of articles published in 1992 to investigate the handling of uncertainty (reference). Of the 63 studies which indicated that their results may have relevance beyond the specific population/context of the study, only 17 failed to consider any form of uncertainty, suggesting that most authors are aware that results of economic evaluations are population/context specific. However, 10 studies which although advised caution of interpretation of their results, failed to consider the likely generalisability of their study through a comprehensive sensitivity analysis.

This research is a step towards development of a framework for critically assessing the generalisability of economic evaluations and for advising on issues to consider in designing, analysing and presenting studies to increase the generalisability of the results. Benefits to the NHS will include increased efficiency in the research commissioning process, improved confidence in using the results of economic evaluation in policy-making and better guidance for researchers in the design, analysis and reporting of studies. Further the National Institute for Clinical Excellence has pointed out that the submission of cost-effectiveness data in support of health technologies need to be relevant to the UK setting, but currently little advice exists on the generalisability approaches to be adopted.

Points for discussion:

Within the spirit of the HESG, this systematic review is work in progress and the first presentation of a checklist developed to enhance transparency and facilitate generalisability within the context of clinical trials.

- Heterogeneity in the quality of reporting (many poor and few good quality)
  - What are the implications for decision-makers regarding current and future policy decisions?
  - Can we health economists help to improve the *state of the art*?
  - Is there any role for peer reviewers to help achieving a higher quality of reports?
  - Is the proposed pro forma developed here a useful starting point?

- We are aware that the proposed *pro forma* may not satisfy the needs of different audiences, and that more work is needed in some parts. For this reason, at the present stage it would be useful for us to identify any missing elements in the checklist.

- Should the checklist be used as a complement to other more general checklists (e.g. BMJ Checklist)

- Finally, this is a generalisability checklist for economic analyses conducted alongside RCTs and an obvious question will be what would a checklist for economic modelling studies contain?

5. References

Adams ME, McCall NT, Gray ET, Orza MJ, Chalmers TC. Economic analysis in randomized controlled trials. Medical Care 1992;30:231-24

Altman DG, Bland JM. Generalisation and extrapolation. British Medical Journal 1998;317:409-410.

Briggs A, Sculpher M. Sensitivity analysis in economic evaluation: a review of published studies. Health Economics 1995; 4(5):355-371

Brouwer WBF, Koopmanschap MA, Rutten FFH. Productivity costs measurement through quality of life? a response to the recommendation of the Washington panel. Health Economics 1997;6:253-259.

Bryan S, Brown J. Extrapolation of cost-effectiveness information to local settings. Journal of Health Services Research and Policy 1998;3:108-112.

Cook J, Drummond M, Glick H, Heyse JF. Analysing economic data from multi-national clinical trials. Issues and recommendations. Paper presented at the Health Economics Research Group meeting, July 1997;

Coyle D, Davies L, Drummond M. Trials and tribulations - emerging issues in designing economic evaluations alongside clinical trials. International Journal of Technology Assessment in Health Care. 1998;14:135-144.

Donaldson C, Birch S, Gafni A. The 'Distribution Problem' in Economic Evaluation: Income Considerations in the Valuation of Costs and Consequences of Health Care Programmes. CHEPA Working Paper 98-10. Hamilton, Ontario: Centre for Health Economics and Policy Analysis, 1998.

Drummond M, Cooke J, Walley T. Economic evaluation under managed competition: evidence from the UK. Social Science Medicine 1997;45:583-595.

Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. British Medical Journal 1996;313:275-283.

Drummond M. Experimental versus observational data in the economic evaluation of pharmaceuticals. Medical Decision Making 1998;18 (suppl):S12-S18.

Drummond MF, Bloom BS, Carrin G, Hillman AL, Hutchings HC, Knill-Jones RP et al. Issues in the cross-national assessment of health technology. International Journal of Technology Assessment in Health Care 1992;8:671-682.

Drummond MF, Davies L. Economic analysis alongside clinical trials. International Journal of Technology Assessment in Health Care 1991;7:561-573.

Drummond MF, Davies L. Economic evaluation of lenograstim for prophylaxis of chemotherapy induced neutropenia in patients with small cell lung cancer. Pharamacoeconomics 1994;6 (suppl 2):44-52.

Drummond MF, Stoddart GL. Economic analysis and clinical trials. Controlled Clinical Trials 1984;5:115-128.
Elixhauser A, Halpern M, Schmier J, Luce BR. Health care CBD and CEA from 1991 to 1996: An updated bibliography. Medical Care 1998;36:MS1-MS9.
Glick HA, Eisenberg JM, Koffer H, Kelley MA, Connell ML. Are cost-effectiveness analyses performed in clinical trials applicable to usual care?: A case study. Medical Decision Making 1988;8:328.
Glick, H., Willke, R., Polsky, D., et al. Economic analysis of tirilazad mesylate for aneurysmal subarachnoid hemorrhage. International Journal of Technology Assessment in Health Care 1998;14(1):145-160
Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.
Heyse J, Cook J, Carides G. Statistical considerations in analysing health care resource utilisation and cost data. . In: Drummond M, McGuire A. (Eds). Economic Evaluation in Health Care – Merging Theory with Practice. Oxford: Oxford University Press, 2001).
Johnston K, Gerard K, Brown J. Generalizing costs from trials. Analyzing center selection bias in a breast screening trial. International Journal of Technology Assessment in Health Care 1998;14:494-504.
Jonnson B, Weinstein M. Economic evaluation alongside multinational clinical trials: study considerations for GUSTO IIb. International Journal of Technology Assessment in Health Care 1997;13:49-58.
Leese B, Hutton J, Maynard A. A comparison of the costs and benefits of recombinant human erythropoietin (epoetin) in the treatment of chronic renal failure in 5 European countries. PharmacoEconomics 1992;1:346-356.
Mason J. The generalisability of pharmacoeconomic studies. Pharmacoeconomics 1997;11:503-514.
Matheson LA, Davies L, Ogg CS, Bosanquet N. Erythropoetin in perspective. Health Policy Unit Review Paper No 6. Cambridge: Daniles Publishing, 1993.
Mauskopf J, Schulman K, Bell L, Glick H. A strategy for collecting pharmacoeconomic data during Phase II/III clinical trials. PharmacoEconomics 1996;264-277.
Menzin J, Oster G, Davies L et al . A multinational economic evaluation of rhDNase in the treatment of cystic fibrosis. International Journal of Technology Assessment 1996;12:52-61.
Miller DK, Homan SM. Determining transition probabilities: confusion and suggestions. Medical Decision Making 1994;14:52-58.
O'Brien BJ. A tale of two (or more) cities: geographic transferability of pharmacoeconomic data. The American Journal of Managed Care 1997;3:S33-S39.
Phelps CE. Good technologies gone bad. How and why the cost-effectiveness of a medical intervention changes for different populations. Medical decision Making 1997;17:107-117.
Pritchard C. Trends in economic evaluation. OHE Briefing no. 36. London: Office of Health Economics, 1998.
Schulman K, Glick H, Buxton M, Sculpher M, Backhouse M, Bell L et al. The economic evaluation of the FIRST study: design of a prospective analysis

alongside a multinational Phase III clinical trial. Controlled Clinical Trials 1996;17:304-315.
Schulman, K, Burke, J., Drummond, M., et al. Resource costing for multinational neurological clinical trials: methods and results. Health Economics 1998;7:629-638
Sculpher MJ, Bryan S, Dwyer N, Hutton J, Stirrat GM. An economic evaluation of transcervical endometrial resection versus abdominal hysterectomy for the treatment of menorrhagia. British Journal of Obstretrics and Gynaecology 1993;100:244-252.
Sculpher MJ, Drummond MF, Buxton MJ. The iterative use of economic evaluation as part of the process of health technology assessment. Journal of Health Servies Research and Policy 1997;2:26-30.
Sculpher MJ, O'Brien BJ. Income Effects of Reduced Health and Health Effects of Rediced Income: Implications for Health State Valuation. Centre for Health Economics and Policy Analysis Working Paper Series 99-02. Hamilton, Ontario: CHEPA, McMaster University, 1999.
Sculpher MJ, Seed P, Henderson RA, Buxton MJ, Pocock SJ, Joy MD et al. Health service costs of coronary angioplasty and coronary artery bypass surgery: the randomised intervention treatment of angina (RITA) trial. Lancet 1994;344:927-929.
Sculpher MJ. A Snip at the Price? AReview of the Economics of Minimal Access Surgery. HERG Discussion Paper Number 11. Uxbridge: HERG, Brunel University, 1993.
Simon G, Wagner E, Vonkorff M. Cost-effectiveness comparisons using "real world" randomized trials: the case of new antidepressant drugs. Journal of Clinical Epidemiology 1995;48:363-373.
Stevens ME, Summerfield GP, Hall AA. Cost benefits of low dose subcutaneouserythropoietin. British Medical Journal 1992;304:474-7.
United States General Accounting Office. Cross Design Synthesis: A New Strategy for Medical Effectiveness Research (GAO/DEMD-98-18). Washington DC: United States General Accounting Office, 1992.
Walker D, Fox-Rushby J. Economic evaluation of parasitic diseases: a critique of the internal and external validity of published studies. Trop Med Int Health 2000;5(4):237-249
Wellwood J, Sculpher MJ, Stoker D et al. Randomised controlled trial of laparoscopic versus open mesh repair for inguinal hernia: outcome and cost. British Medical Journal 1998;317:103-110.
Willke RJ, Glick H, Polsky D, Schulman K. Estimating country-specific cost-effectiveness from multinational clinical trials. Health Economics 1998;7:481-493.

Studies included in the review

Armstrong S H, Ruckley C V. Use of a fibrous dressing in exuding leg ulcers. Journal of Wound Care 1997; 6(7); 322-4
Bailey T C, Ritchie D J, McMullin S T, Kahn M, Reichley R M, Casabar E, Shannon W, Dunagan W C. A randomized, prospective evaluation of an interventional program to discontinue intravenous antibiotics at two tertiary care teaching institutions. Pharmacotherapy 1997; 17(2); 277-281
Bennett-Guerrero E, Sorohan J G, Gurevich M L, Kazanjian P E, Levy R R,

Barbera A V, White W D, Slaughter T F, Sladen R N, Smith P K, Newman M F. Cost-benefit and efficacy of aprotinin compared with epsilon-aminocaproic acid in patients having repeated cardiac operations:a randomized, blinded clinical trial. Anesthesiology 1997; 87(6); 1373-1380

Boccalon H, Elias A, Chale J-J, Cadene A, Gabriel S for the Vascular Midi-Pyrenees Network Group. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees Study. Archives of Internal Medicine 2000; 160; 1769-1773

Booth P C, Wells N E J, Morrison A K. A comparison of the cost effectiveness of alternative prophylactic therapies in childhood asthma. PharmacoEconomics 1996; 10(3); 262-268

Burton L C,Steinwachs D M,German P S,Shapiro S,Brant L J, RichardsTM,Clark R D. Preventive services for the elderly:would coverage affect utilisationand costs under Medicare? American Journal of Public Health 1995; 85(3); 387-391

Bytzer P, Moller Hansen J M, Schaffalitzky de Muckadell O B. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia..Lancet 1994; 343(8901); 811-816

Canard J M, Cellier C, Houcke P, Laurent J, Gorce D, Landi B. Prospective multicentre study comparing a standard reusable sphincterotome with a disposable triple-lumen sphincterotome. Gastrointestinal Endoscopy 2000; 51(6); 704-707

Choiniere M, Rittenhouse B E, Perreault S, Chartrand D, Rousseau P, Smith B, Pepler C. Efficacy and costs of patient-controlled analgesia versus regularly administered intramuscular opioid therapy. Anesthesiology 1998; 89(6); 1377-1388

Dasbach E J, Rich M W, Segal R, Gerth W C, Carides G W, Cook J R, Murray J F, Snavely D B, Pitt B. The cost-effectiveness of losartan versus captopril in patients with symptomatic heart failure. Cardiology 1999; 91(3); 189-194

Davey P, Craig A M, Hau C, Malek M. Cost-effectiveness of prophylactic nasal mupirocin in patients undergoing peritoneal dialysis based on a randomized, placebo-controlled trial. Journal of Antimicrobial Chemotherapy 1999; 43(1); 105-112

Detournay B, Huet X, Fognani F, Montalescot G. Economic evaluation of enoxaparin sodium versus heparin in unstable angina: a French sub-study of the ESSENCE trial. Pharmacoeconomics 2000; 18(1); 83-89

Ellis S L, Carter B L, Malone D C, Billups S J, Okano G J, Valuck R J, Barnette D J, Sintek C D, Covey D, Mason B, Jue S, Carmichael J, Guthrie K, Dombrowski R, Geraets D R, Amato M. Clinical and economic impact of ambulatory care clinical pharmacists in management of dyslipidemia in older adults: the IMPROVE study. Pharmacotherapy 2000; 20(12); 1508-1516

Erhardt L, Ball S, Andersson F, Bergentoft P, Martinez C. Cost effectiveness in the treatment of heart failure with ramipril: a Swedish substudy of the AIRE study. (published erratum appears in Pharmacoeconomics 1997;12(6):706) Pharmacoeconomics 1997; 12(2); 256-266)

Fagnani F, Bouvenot G, Valat J-P, Bardin T, Berdah L, Lafuma A, Bone I,

Eschwege E, Dresier R-L. Medico-economic analysis of diacerein with or without standard therapy in the treatment of osteoarthritis. Pharmacoeconomics 1998; 13(1 Part 2); 135-146

Franz M J, Splett P L, Monk A, Barry B, McClain K, Weaver T, Upham P, Bergenstal R, Mazze R S. Cost-effectiveness of medical nutrition therapy provided by dietitians for persons with non-insulin-dependent diabetes mellitus. Journal of the American Dietetic Association 1995; 95(9); 1018-1024

Friedman M, Serby C W, Menjoge S S, Wilson J D, Hilleman D E, Witek T J. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest 1999; 115(3); 635-641

Gafni A, Goeree R, Myhr T L, Hannah M E, Blackhouse G, Willan A R, Weston J A, Wang E E L, Hodnett E D, Hewson S A, Farine D, Ohlsson A. Induction of labour versus expectant management for prelabour rupture of the membranes at term: an economic evaluation. Canadian Medical Association Journal 1997; 157(11); 1519-1525

Glick H, Willke R, Polsky D, Llana T, Alves W M, Kassell N, Schulman K. Economic analysis of tirilazad mesylate for aneurysmal subarachnoid hemorrhage: economic evaluation of a phase III clinical trial in Europe and Australia. International Journal of Technology Assessment in Health Care 1998; 14(1); 145-160

Gournay K, Brooking J. The community psychiatric nurse in primary care: an economic analysis Journal of Advanced Nursing 1995; 22; 769-778

Grampian Asthma Study of Integrated Care (GRASSIC) (Drummond N, Abdall M, Buckingham J K, Beattie J A G, Lindsay T, Osman L M, Ross S J, Roy-Chaudhury A, Russell I, Turner M, Douglas J G, Legge J S, Friend J A R). Integrated Care for Asthma - A Clinical, Social, and Economic Evaluation. BMJ 1994; 308; 559-564

Gray A, Raikou M, McGuire A, Fenn P, Stevens R, Cull C, Stratton I, Adler A, Holman R, Turner R on behalf of the United Kingdom Prospective Diabetes Study Group. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). BMJ 2000; 320; 1373-1378

Griffiths R I, Anderson G F, Powe N R, Oliveras E, Herbert R J, Grant CC, Davidson B L. Economic impact of immunization against rotavirus gastroenteritis: evidence from a clinical trial. Archives of Pediatrics and Adolescent Medicine 1995; 149(4); 407 414

Grines C L, Marsalese D L, Brodie B, Griffin J, Donohue B, Constantini C R, Balestrini C, Stone G, Wharton T, Esente P, Spain M, Moses J, Nobuyoshi M, Ayres M, Jones D, Mason D, Sachs D, Grines L L, O'Neill W. Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. Journal of the American College of Cardiology 1998; 31(5); 967-972

Grossman R, Mukherjee J, Vaughan D, Eastwood C, Cook R, LaForge J, Lampron N. A 1-year community-based health economic study of ciprofloxacin vs usual antibiotic treatment in acute exacerbations of chronic bronchitis:the Canadian Ciprofloxacin Health Economic Study

Group. Chest 1998; 113(1); 131-141
Grunfeld E, Gray A, Mant D, Yudkin P, Adewuyi-Dalton R, Coyle D, Cole D, Stewart J, Fitzpatrick R, Vessey M. Follow up of breast cancer in primary care vs specialist care: results of an economic evaluation. British Journal of Cancer 1999; 79(7-8); 1227-1233
Guthrie E, Moorey J, Margison F, Barker H, Palmer S, McGrath G, Tomenson B, Creed F. Cost-effectiveness of brief psychodynamic-interpersonal therapy in high utilizers of psychiatric services. Archives of General Psychiatry 1999; 56(6); 519-526
Hamilton S H, Revicki D A, Edgell E T, Genduso L A, Tollefson G. Clinical and economic outcomes of olanzapine compared with haloperidol for schizophrenia: results from a randomised clinical trial. Pharmacoeconomics 1999; 15(5); 469-480
Hansson C. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. International Journal of Dermatology 1998; 37(5); 390-396
Harrington R, Peters S, Green J, Byford S, Woods J, McGowan R. Randomised comparison of the effectiveness and costs of community and hospital based mental health services for children with behavioural disorders. BMJ 2000; 321; 1-5
Harvey I, Nelson S J, Lyons R A, Unwin C, Monaghan S, Peters T. A randomized controlled trial and economic evaluation of counselling in primary care. British Journal of General Practice 1998; 48; 1043-1048
Hillman A L, Schwartz J S, Willian M K, Peskin E, Roehrborn C G, Oesterling J E, Mason M F, Maurath C J, Deverka P A, Padley R. The cost-effectiveness of terazosin and placebo in the treatment of moderate to severe benign prostatic hyperplasia. Urology 1996; 47(2); 169-178
Hull R D, Raskob G E, Rosenbloom D, Pineo G F, Lerner R G, Gafni A, Trowbridge A A, Elliott C G, Green D, Feinglass J, Feldstein W, Brant R. Treatment of proximal vein thrombosis with subcutaneous low-molecular-weight heparin vs intravenous heparin. Archives of Internal Medicine 1997; 157; 289-294
Hutchins S S, Rosenthal J, Eason P, Swint E, Guerrero H, Hadler S. Effectiveness and cost-effectiveness of linking the special supplemental program for women, infants, and children (WIC) and immunization activities. Journal of Public Health Policy 1999; 20(4); 408-426
Jones R, Tait C, Sladen G, Weston-Baker J. A trial of a test-and-treat strategy for helicobacter pylori positive dyspeptic patients in general practice. International Journal of Clinical Practice 1999; 53(6); 413-416
Jonsson B, Cook J R, Pedersen T R. The cost-effectiveness of lipid lowering in patients with diabetes results from the 4S trial. Diabetologia 1999; 42(11); 1293-1301
Jonsson B, Johannesson M, Kjekshus J, Olsson A G, Pedersen T R, Wedel H. Cost-effectiveness of cholesterol lowering: results from the Scandinavian Simvastatin Survival Study (4S). European Heart Journal 1996; 17(7); 1001-1007
Kald A, Anderberg B, Carlsson P, Park P O, Smedh K. Surgical outcome and cost-minimisation-analyses of laparoscopic and open hernia repair:a randomised prospective trial with one year follow up. European Journal of

Surgery 1997; 163(7); 505-510
Karalus, N C, Garrett, J E, Lang, S D R, Scott, W G, Leng, RA, Kostalas, G N, Cursons, R T M, Cooper, B C, Scott, H M. A clinical and economic comparison of roxithromycin 150 mg twice daily vs amoxicillin 500mg/calvulanic acid 125mg three times daily for the treatment of lower respiratory tract infections in general practice. Drug Investigation 1994; 8(3); 179-190
Laloux P, Vakaet A, Monseu G, Jacquy J, Bourgeois P, van der Linden C. Subcutaneous sumatriptan compared with usual acute treatments for migraine: clinical and pharmacoeconomic evaluation. Acta Neurologica Belgica 1998; 98(4); 332-341
Lawrence K, McWhinnie D, Goodwin A, Gray A, Gordon J, Storie J, Britton J, Collin J. An economic evaluation of laparoscopic versus open inguinal hernia repair. Journal of Public Health Medicine 1996; 18(1); 41-48
LePen C, Lilliu H, Keller T, Fiessinger S. The economics of TRACE:a cost-effectiveness analysis of trandolapril in postinfarction patients with left ventricular dysfunction. Pharmacoeconomics 1998; 14(1); 49-58
Liem M S L, Halsema J A M, Van der Graaf Y, Schrijvers A J P, van Vroonhoven T J M V. Cost-effectiveness of extraperitoneal laparoscopic inguinal hernia repair:a randomized comparison with conventional herniorrhaphy. Annals of Surgery 1997; 226(6); 668-675
Liljas B, Stahl E, Pauwels R A. Cost effectiveness analysis of a dry powder inhaler (Turbuhaler) versus a pressurised metered dose inhaler in patients with asthma. Pharmacoeconomics 1997; 12(2); 267-277
Lundback B, Jenkins C, Price M J, Thwaites R M A. Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 mu g twice daily and budesonide 800 mu g twice daily in the treatment of adults and adolescents with asthma. Respiratory Medicine 2000; 94(7); 724-732
Malmivaara A, Hakkinen U, Aro T, Heinrichs M L, Koskenniemi L, Kuosma E, Lappi S, Paloheimo R, Servo C, Vaaranen V, Hernberg S. The treatment of acute low back pain: bed rest, exercises, or ordinary activity? New England Journal of Medicine 1995; 332(6); 351-355
Mark D B, Cowper P A, Berkowitz S D, Davidson-Ray L, DeLong E R, Turpie A G G, Califf R M, Weatherley B, Cohen M. Economic assessment of low-molecular-weight heparin (enoxaparin) versus unfractionated heparin in acute coronary syndrome patients: results from the ESSENCE randomized trial. Circulation 1998; 97(17); 1702-1707
Mark D B, Harrington R A, Lincoff A M, Califf R M, Nelson C L, Tsiatis A A, Buell H, Mahaffey K W, Davidson-Ray L, Topol E J. Cost-effectiveness of platelet glycoprotein IIb/IIIa inhibition with eptifibatide in patients with non-ST-elevation acute coronary syndromes. Circulation 2000; 101(4); 366-371
Martinez C, Ball S G. Cost-effectiveness of ramipril therapy for patients with clinical evidence of heart failure after acute myocardial infarction. British Journal of Clinical Practice 1995; Supplement 78; 26-32
Meenan R T, Stevens V J, Hornbrook M C, La Chance P-A, Glasgow R E, Hollis J F, Lichtenstein E, Vogt T M. Cost-effectiveness of a hospital-based smoking cessation intervention. Medical Care 1998; 36(5); 670-678
Mol B W J, Hajenius P J, Engelsbel S, Ankum W M, Hemrika D J, Van der Veen

F, Bossuyt P M M. Treatment of tubal pregnancy in the Netherlands: an economic comparison of systemic methotrexate administration and laparoscopic salpingostomy. American Journal of Obstetrics & Gynecology 1999; 181(4); 945-951

Monteon F, Correa-Rotter R, Paniagua R, Amato D, Hurtado M E, Medina JL, Salcedo R M, Garcia E, Matos M, Kaji J, Vazquez R, Ramos A, Schettino M A, Moran J. Prevention of peritonitis with disconnect systems in CAPD: a randomised controlled trial. Kidney International 1998; 54(6); 2123-2128

Morrell C J, Walters S J, Dixon S, Collins K A, Brereton L M L, Peters J, Brooker C G D. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. BMJ 1998; 316; 1487-1491

Murphy M A, Maze N M, Boyd J L, Quick D C, Buss D D. Cost-benefit comparison: holmium laser versus electrocautery in arthroscopic acromioplasty. Journal of Shoulder & Elbow Surgery 1999; 8(3); 275-278

Naylor M D, Brooten D, Campbell R, Jacobsen R, Mezey M D, Pauly M V, Schwartz J S. Comprehensive discharge planning and home follow-up of hospitalised elders: a randomized clinical trial. JAMA 1999; 281(7); 613-620

Nicolle L E, Kirshen A, Boustcha E, Montgomery P. Treatment of moderate-to-severe pneumonia in elderly, long-term care facility residents. Infectious Diseases in Clinical Practice 1996; 5(2); 130-136

Nord E, Wisloff F, Hjorth M, Westin J. Cost-utility analysis of melphalan plus prednisone with or without interferon-Alpha2b in newly diagnosed multiple myeloma: results from a randomised controlled trial. Pharmacoeconomics 1997; 12(1); 89-103

O'Brien B, Levine M, Willan A, Goeree R, Haley S, Blackhouse G, Gent M. Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. Archives of Internal Medicine 1999; 159; 2298-2304

O'Byrne P, Cuddy L, Taylor D W, Birch S, Morris J, Syrotuik J. Efficacy and cost benefit of inhaled corticosteroids in patients considered to have mild asthma in primary care practice. Canadian Respiratory Journal 1996; 3(3); 169-175

Oster G, Huse D M, Lacey M J, Regan M M, Fuchs H J. Effects of recombinant human dnase therapy on healthcare use and costs in patients with cystic fibrosis. Annals of Pharmacotherapy. 1995; 29(5); 459-464

Paganini A M, Lezoche E, Carle F, Carlei F, Favretti F, Feliciotti F, Gesuita R, Guerrieri M, Lomanto D, Nardovino M, Panti M, Ribichini P, Sarli L, Sottili M, Tamburini A, Taschieri A. A randomized, controlled, clinical study of laparoscopic vs open tension-free inguinal hernia repair. Surgical Endoscopy - Ultrasound & Interventional Techniques 1998; 12(7); 979-986

Pedersen T R, Kjekshus J, Berg K, Olsson A G, Wilhelmsen L, Wedel H, Pyorala K, Miettinen T, Haghfelt T, Faergeman O, Thorgeirsson G, Jonsson B, Schwartz J S. Cholesterol lowering and the use of healthcare resources:results of the Scandinavian simvastatin survival study. Circulation 1996; 93(10); 1796-1802

Pelc A, Portier H, Gehanno P, Fiessinger S, Ichou F. Cost saving of 5-day therapy with cefpodoxime proxetil versus standard 10-day beta-lactam therapy for recurrent pharyngotonsillitis in adults. PharmacoEconomics

1996; 10(3); 239-250
Petrou S, Coyle D, Fraser W D. Cost-effectiveness of a delayed pushing policy for patients with epidural anesthesia. American Journal of Obstetrics & Gynecology 2000; 182(5); 1158-1164
Poynard T, Ottignon Y, Pauphilet C, Agostini H. A randomized trial of the usefulness of endoscopy after an initial treatment of non-severe esophagitis. Gastroenterologie Clinique et Biologique 1997; 21(6-7); 497-502
Poynard T, Vernisse B, Agostini H. Randomized, multicentre comparison of sodium alginate and cisapride in the symptomatic treatment of uncomplicated gastro-oesophageal reflux. Alimentary Pharmacology & Therapeutics 1998; 12(2); 159-165
Rabah M, Mason D, Muller D W M, Hundley R, Kugelmass A D, Weiner B, Cannon L, O'Neill W W, Safian R D. Heparin after percutaneous intervention (HAPI): a prospective multicenter randomized trial of three heparin regimens after successful coronary intervention. Journal of the American College of Cardiology 1999; 34(2); 461-467
Rajan R, Gafni A, Levine M, Hirsh J, Gent M. Very low-dose warfarin prophylaxis to prevent thromboembolism in women with metastatic breast cancer receiving chemotherapy: an economic evaluation. Journal of Clinical Oncology 1995; 13(1); 42-46
Rodriguez A, Ayala F, Bernardi V, Santaera O, Marchand E, Pardinas C, Mauvecin C, Vogel D, Harrell L C, Palacios I F. Optimal coronary balloon angioplasty with provisional stenting versus primary stent (OCBAS):immediate and long-term follow-up results. Journal of the American College of Cardiology 1998; 32(5); 1351-1357
Roseveare C D, Patel P, Simmonds N, Goggin P M, Kimble J, Shepherd H A. Metal stents improve dysphagia, nutrition and survival in malignant oesophageal stenosis:a randomized controlled trial comparing modified Gianturco Z-stents with plastic Atkinson tubes. European Journal of Gastroenterology & Hepatology 1998; 10(8); 653-657
Rutten-van Molken M P M H, van Doorslaer E K A, Till M D. Cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma. Pharmacoeconomics 1998; 14(6); 671-684
Sacristan J A, Kennedy-Martin T, Rosell R, Cardenal F, Anton A, Lomas M, Alberola V, Massuti B, Carrato A, Minshall M. Economic evaluation in a randomized phase III clinical trial comparing gemcitabine/cisplatin and etoposide/cisplatin in non-small cell lung cancer. Lung Cancer 2000; 28(2); 97-107
Sanchez Garcia M, Cambronero Galache J A, Lopez Diaz J, Cerda Cerda E, Rubio Blasco J, Gomez Aguinaga M A, Nunez Reiz A, Rogero Marin S, Onoro Canaveral J J, Sacristan del Castillo J A. Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients:a randomized, double-blind, placebo-controlled, multicenter trial. American Journal of Respiratory & Critical Care Medicine 1998; 158(3); 908-916
Schmidt-Matthiesen A, Roding H, Windolf J, Sommerfeldt D, Gutt C, Pannike A, Encke A. A prospective, randomised comparison of single-vs. multiple-dose antibiotic prophylaxis in penetrating trauma. Chemotherapy 1999;

45(5); 380-391
Schnitzler M A, Woodward R S, Lowell J A, Singer G G, Brennan D C. High risk kidney transplant rejection treatment: cost savings from thymoglobulin. Transplantation Proceedings 1999; 31(1-2); 269-271
Schulman K A, Buxton M, Glick H, Sculpher M, Guzman G, Kong J, Backhouse M, Mauskopf J, Bell L, Eisenberg J M. Results of the economic evaluation of the First Study: a multinational prospective economic evaluation. International Journal of Technology Assessment in Health Care 1996; 12(4); 698-713
Schulman K A, Dorsainvil D, Yabroff K R, DiCesare J, Felser J, Eisenberg J M, Glick H A. Prospective economic evaluation accompanying a trial of GM-CSF/IL-3 in patients undergoing autologous bone marrow transplantation for Hodgkins and non-Hodgkins-lymphoma. Bone Marrow Transplantation 1998; 21(6); 607-614
Scott W G,Cooper B C,Scott H M. Pharmacoeconomic evaluation of roxithromycin versus amoxycillin clavulanic acid in a community-acquired lower respiratory tract infection study. Infection 1995; 23(Supplement 1); S21-S24
Sculpher M J, Seed P, Henderson R A , Buxton M J, Pocock S J, Parker J, Joy M D, Sowton E, Hampton J R. Health service costs of coronary angioplasty and coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. Lancet 1994; 344(8927); 927-933
Serruys P W, van Hout B, Bonnier H, Legrand V, Eulogio Garcia, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, an Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel M-A. For the Benestent Study Group. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet 1998; 352; 673-681
Severens J L, Prahl C, Kuijpers-Jagtman A M, Prahl-Andersen B. Short-term cost-effectiveness analysis of presurgical orthopedic treatment in children with complete unilateral cleft lip and palate. Cleft Palate-Craniofacial Journal 1998; 35(3); 222-226
Severson H H, Andrews J A, Lichtenstein E, Wall M, Akers L. Reducing maternal smoking and relapse: long-term evaluation of a pediatric intervention. Preventive Medicine 1997; 26; 120-130
Skargren E I, Oberg B E, Carlsson P G, Gade M. Cost and effectiveness analysis of chiropractic and physiotherapy treatment for low back and neck pain: six-month follow-up. Spine 1997; 22(18); 2167-2177
Stone G W, Grines C L, Rothbaum D, Browne K F, O'Keefe J, Overlie P A, Donohue B C, Chelliah N, Vlietstra R, Catlin T, O'Neill W W. Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator:the primary angioplasty in myocardial infarction (PAMI) trial. Journal of the American College of Cardiology 1997; 29(5); 901-907
Suver J, Arikian S R, Doyle J J, Sweeney S W, Hagan M. Use of anesthesia selection in controlling surgery costs in an HMO Hospital. Clinical Therapeutics 1995; 17(3); 561-571

Sweat M, Gregorich S, Sangiwa G, Furlonge C, Balmer D, Kamenga C, Grinstead O, Coates T. Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. Lancet 2000; 356; 113-121

The Canadian Lung Oncology Group. Investigation for mediastinal disease in patients with apparently operable lung cancer. Annals of Thoracic Surgery 1995; 60(5); 1382-1389

Torrance G, Walker V, Grossman R, Mukherjee J, Vaughan D, La Forge J, Lampron N. Economic evaluation of ciprofloxacin compared with usual antibacterial care for the treatment of acute exacerbations of chronic bronchitis in patients followed for 1 year. Pharmacoeconomics 1999; 16(5 Part 1); 499-520

Tsevat J, Duke D, Goldman L, Pfeffer M A, Lamas G A, Soukup J R, Kuntz KM, Lee T H. Cost-effectiveness of captopril therapy after myocardial infarction. Journal of the American College of Cardiology 1995; 26(4); 914-919

van Bergen P F M M, Jonker J J C, van Hot B A, van Domburg R T, Deckers J W, Azar A J, Hofman A. Costs and effects of long-term oral anticoagulant treatment after myocardial infarction. JAMA 1995; 273(12); 925-928

van Dijk L C, Seerden R, van Urk H, Wittens C H A. Comparison of cost affecting parameters and costs of the "closed" and "open" in situ bypass technique. European Journal of Vascular & Endovascular Surgery 1997; 13(5); 460-463

Venning P, Durie A, Roland M, Roberts C, Leese B. Randomised controlled trial comparing cost effectiveness of general practitioners and nurse practitioners in primary care. BMJ 2000; 320; 1048-1053

Vergnenegre A, Perol M, Pham E, Balmes P, Blanchon F, Bonnaud F, Carles P, Clavier J, Guerin J C, Kleisbauer J P, Muir J F, Paillotin D, Poirier R, Taytard A. Cost analysis of hospital treatment:two chemotherapic regimens for non-surgical non-small cell lung cancer. Lung Cancer 1996; 14(1); 31-44

Weaver W D, Reisman M A, Griffin J J, Buller C E, Leimgruber P P, Henry T, D'Haem C, Clark V L, Martin J S, Cohen D J, Neil N, Every N R for the OPUS-1 Investigators. Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): a randomised trial. Lancet 2000; 355; 2199-2203

Webb A, Cunningham D, Scarffe J H, Harper P, Norman A, Joffe J K, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M. Randomised trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. Journal of Clinical Oncology 1997; 15(1); 261-267

Weintraub W S, Culler S, Boccuzzi S J, Cook J R, Kosinski A S, Cohen DJ, Burnette J. Economic impact of GPIIB/IIIA blockade after high-risk angioplasty: results from the RESTORE trial. Journal of the American College of Cardiology 1999; 34(4); 1061-1066

Wever E F D, Hauer R N W, Schrijvers G, van Capelle F J L, Tijssen J G P, Crijns H J G M, Algra A, Ramanna H, Bakker P F A, Demedina E O R. Cost-effectiveness of implantable defibrillator as first-choice therapy

versus electrophysiologically guided, tiered strategy in postinfarct sudden death survivors: a randomized study. Circulation 1996; 93(3); 489-496
White D J, Billingham C, Chapman S, Drake S, Jayaweera D, Jones S, Opaneye A, Temple C. Podophyllin 05% or 20% v podophyllotoxin 05% for the self treatment of penile warts:a double blind randomised study. Genitourinary Medicine 1997; 73(3); 184-187
Wolter J M, Bowler S D, Nolan P J, McCormack J G. Home intravenous therapy in cystic fibrosis:a prospective randomised trial examining clinical, quality of life and cost aspects. European Respiratory Journal 1997; 10(4); 896-900
Wootton R, Bloomer S E, Corbett R, Eedy D J, Hicks N, Lotery H E, Mathews C, Paisley J, Steele K, Loane M A. Multicentre randomised control trial comparing real time teledermatology with conventional outpatient dermatological care: societal cost-benefit analysis. BMJ 2000; 320; 1252-1256

Studies excluded from the review

Bassan R, Lerede T, Di Bona E, Rossi G, Pogliani E, Rambaldi A, Buelli M, Viero P, Rodeghiero F, Izzi T, Corneo G, Barbui T. Granulocyte colony-stimulating factor (G-CSF, Filgrastim) after or during an intensive remission induction therapy for adult acute lymphoblastic leukaemia:effects, role of patient pre-treatment characteristics, and costs. Leukemia & Lymphoma 1997; 26(1-2); 153-161
Cunningham D, Gore M, Davidson N, Miocevich M, Manchanda M, Wells N. The real costs of emesis: an economic analysis of ondansetron vs metoclopramide in controlling emesis in patients receiving chemotherapy for cancer. European Journal of Cancer: Part A 1993; 29(3); 303-306
Ellis E, Koblin W, Irvine M J, Legare J, Logan A G. Small, blue collar work site hypertension screening: a cost-effectiveness study. Journal of Occupational Medicine 1994; 36(3); 346-355
Houcke P, Maffioli C, Corallo J, Bouxinsauzet A, Martin A L. Comparison of rocgel(r) with an h-2-antihistamine on the symptomatology of gastroesophageal reflux without esophagitis [Comparaison du Rocgel et d'un anti-H2 sur la symptomatologie du reflex gastro-oesophagien sans oesophagite] [French]. Annales de Gastroenterologie et d'Hepatologie 1995; 31(4); 264-267
Kumpusalo E, Neittaanmaki L, Halonen P, Pekkarinen H, Penttila I, Parviainen M. Finnish healthy village study: impact and outcomes of a low-cost local health promotion programme. Health Promotion International 1996; 11(2); 105-115
Naglak M, Mitchell D C, Kris-Etherton P, Harkness W, Pearson T A. What to consider when conducting a cost-effectiveness analysis in a clinical setting. Journal of the American Dietetic Association 1998; 98(10); 1149-1154

Appendix:

Checklist used for the present review of trial-based economic evaluations

Data presentation and reporting

1) Reference citation ***(Please write)***				
2) Type of Randomised Trial *(Please tick)*	❑ Single centre ❑ Multi-centre (national) ❑ Multinational			
3) Economic study type *(Please tick all that apply)*	❑ Cost Effectiveness Analysis ❑ Cost Utility Analysis ❑ Cost Benefit Analysis ❑ Cost Consequence Analysis ❑ Cost Minimization Analysis			
4) What is the study question? *(Please fill in)*				
5) What are the population and intervention(s) *(Please tick)*	❑ Population Please, specify_____ ❑ Main intervention(s) Please, specify_____ ❑ Comparator(s) Please specify_____			
6) On what basis is sampling undertaken?		Resource use	Clinical Outcome	HRQoL
	Patients			
	Centres			
	Countries			
	Data collected outside trial			

7) If multi national / multi centre trial please report the number of centres involved.		Cost	Effectiveness
	No. of centres		
	No. of patients		
	No. of countries / jurisdictions		
8) Country or countries where the economic study was carried out *(Please write)*			
9) Were the alternatives described and justified?	❑ Described and justified ❑ Described (only) ❑ No		
10) Were the study inclusion and exclusion criteria for the study population described?	❑ Yes ❑ No		
11a) Were the study sample baseline characteristics described?	❑ Yes ❑ No		
11b) If Yes, please tick where appropriate	❑ Age ❑ Gender ❑ Co-morbidities ❑ Life-style habits (eg. Smokers) ❑ Ethnic group ❑ Disease Severity ❑ Other Clinical ❑ Other, please specify_____		
12) Was any attempt made to assess whether the study sample was representative of the study population?	❑ Yes ❑ No		
13) Was the economic study perspective defined?	❑ Yes ❑ No		

14) Was the analysis consistent with the study perspective?	❑ Yes ❑ No ❑ N/A If no, please give details
15) Was the study setting specified (eg. Type of facility)?	❑ Yes ❑ No
16) Were the prevalence or incidence of the disease reported (for prevention or detection studies)?	❑ Yes ❑ No ❑ Not relevant
17) Was any information provided on the health care system(s) where the trial was conducted?	❑ Yes ❑ No
18) Were centre-specific characteristics reported?	❑ Yes ❑ No If yes, please say which: ❑ Professionals' experience ❑ Teaching hospital ❑ Size of the centre ❑ Volume of cases per year ❑ Other_____
<u>19) Was the duration of the recruitment period reported?</u> **20) Was the duration of the follow up period reported?**	❑ Yes ❑ No ❑ Yes ❑ No

21) Were the following details about unit costs provided? ▪ **Currency** ▪ **Year of costing** ▪ **Sources**	❑ Yes ❑ No ❑ Yes ❑ No ❑ Yes ❑ Partially ❑ No
22) Were unit costs and resource use reported separately?	❑ Yes ❑ No ❑ Partially
23) Were details of currency conversion provided?	❑ Yes ❑ No ❑ Not relevant
24) Were sources of preference data specified?	❑ If yes, which one ❑ Public ❑ Patients ❑ Others_____ ❑ No ❑ Not relevant
25) Was the geographical location of the preference sample stated?	❑ Yes ❑ No

Analytical methods relating to generalisability within the trial

26) Did the authors compare their results with other similar studies?	❑ Yes ❑ No
27a) Were any quantitative analyses conducted to explore variability in results from place to place? **If yes, please give details**	❑ Yes ❑ No
27b) Were any descriptive analyses conducted to explore variability in results from place to place? **If yes, please give details**	❑ Yes ❑ No
28a) Were any quantitative analyses conducted to explore variability in results over time? **If yes, please give details**	❑ Yes ❑ No
28b) Were any descriptive analyses conducted to explore variability in results over time? **If yes, please give details**	❑ Yes ❑ No
29a) Were any quantitative analyses conducted to explore variability in results between study and practice (eg. Protocol driven resources, compliance)? **If yes, please give details**	❑ Yes ❑ No

29b) Were any descriptive analyses conducted to explore variability in results between study and practice (eg. Protocol driven resources, compliance)? **If yes, please give details**	❑ Yes ❑ No
30) What are the sources of variation identified by the authors? *(Please tick any that apply)*	❑ No analysis undertaken ❑ None identified ❑ Compliance ❑ Patients case-mix ❑ Demography ❑ Epidemiology ❑ Clinical practice ❑ Absolute/relative costs (prices) ❑ Individual preferences ❑ Opportunity cost of resources ❑ Capacity scale and joint production ❑ Learning effect ❑ Organization ❑ Timing in life cycle of the technology ❑ Other_____
31) Do the authors set the results in context to other independent interventions (e.g. in a CE-league table)?	❑ Yes ❑ No
32) Please give other relevant information if deemed necessary *(Please fill in)*	

Analytical methods to adjust trial results to non-trial context(s)

33) Were analyses undertaken to adjust the results from trial locations to non-trial locations? **If yes, please give details.**	❑ Yes ❑ No
34) Were analyses undertaken to adjust the results from study to practice outside the trial? **If yes, please give details.**	❑ Yes ❑ No
35) Were analyses undertaken to adjust the results to different time points? **If yes, please give details.**	❑ Yes ❑ No